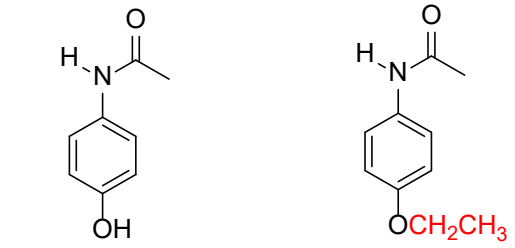
# The Synthesis of Phenacetin from Acetaminophen

## Introduction

Acetaminophen, also known as paracetamol, and phenacetin (both shown in Figure 1) are non-opioid analgesics. Acetaminophen was first synthesized in 1877, and first used in humans in 1887. It is the most widely used, non-anti-inflammatory medication for mild to moderate pain relief and fever reduction. Phenacetin is an analog of acetaminophen and was utilized for nearly 100 years until the FDA banned its use in 1983 and all products it was contained in. Although it was effective as a non-opioid analgesic, physicians and the FDA had concerns with its carcinogenic properties as well as its negative effects on the kidneys.

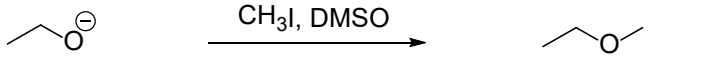
*Figure 1. The structures of acetaminophen and phenacetin*




acetaminophen phenacetin

The synthesis of phenacetin from acetaminophen will be accomplished via the Williamson-ether synthesis. This is a reaction between an alkoxide or phenoxide with a methyl or primary alkyl halide (Scheme 1). Scheme 1 depicts an ethoxide reacting with methyl iodide to yield the compound ethyl methyl ether.

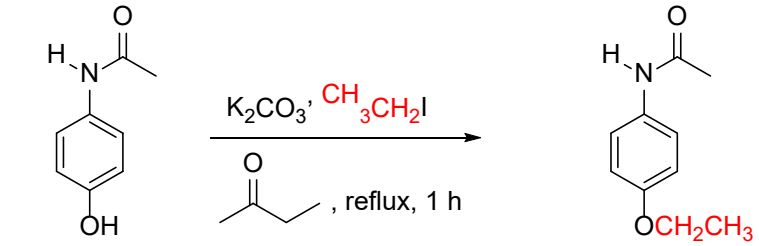
*Scheme 1. The synthesis of an ether via the Williamson-ether reaction*




ethoxide ethyl methyl ether

Scheme 2 shows the reaction that will be performed in this experiment. Acetaminophen is treated

*Scheme 2. Phenacetin synthesized from acetaminophen using potassium carbonate*




acetaminophen phenacetin

with anhydrous potassium carbonate and ethyl iodide, while 2-butanone is employed as the solvent. The reaction is heated at reflux for 1 hour and then put through a series of workup steps.

Pre-lab Questions:

1. What kind of solvent is used in this reaction? Polar protic, etc?
2. What is the role of potassium carbonate?
3. What is the name of the mechanism that this undergoes? E1, etc.
4. What is the theoretical yield of the product?

Prelab Outline:

Make sure to outline a good prelab so you could perform the experiment without this handout. Your table of reagents should, as always, have mass, mmol, volume used (if applicable), physical properties (mp, bp, densities if applicable, etc.), and any hazards, of course.

**The Procedure**:

1. Set hot plate to 225 +/- 5 °C.
2. Add acetaminophen (500 mg), $K_2CO_3$ (665 mg), and 2-butanone (aka. methyl ethyl ketone, 7 mL) to a 25 mL RBF. Please note that the $K_2CO_3$ will not dissolve. Add ethyl iodide (0.64 mL) via syringe followed by the football-shaped magnetic stir bar.
3. Turn the stirrer on to low. The stir bar should be allowed to spin at a rate to sufficiently mix the heterogeneous solution.
4. Attach water jacketed condenser and reflux for 1 hour. Do not start timing until the solution has reached reflux. Clamp the neck of the RBF, not the condenser.
    a. Remember water goes in the bottom and out the top.
    b. Attach a clamp holder to the end of the drain tube to keep it weighted in the drain.
    c. Turn water to a trickle. If it is slowly draining, it is high enough.
5. After 1 hour has expired, raise your apparatus out of the aluminum block, remove block from the hot plate (USE HAND PROTECTION!), reduce heat to 50 °C and let the RBF cool to the touch.

**Reaction Work Up:**

1. Add 4 mL water to the RBF and allow the solid to dissolve.
2. Turn off the stirring and transfer the contents to a 25x100 mm culture tube. This will be called the X-large culture tube, or XLCT, and can be found on the common equipment bench.
3. Rinse RBF with tert-butyl methyl ether (TBME, 4 x 1 mL) and add each rinse to the tube.
4. Remove bottom (aqueous) layer and place into centrifuge tube.
5. Backwash the centrifuge tube with TBME (1 x 2.5 mL). Mix layers well with pipet, allow layers to separate, remove lower layer and place into a waste beaker. Add the organic layer to the XLCT.
6. Extract contents of XLCT with 5% NaOH (2 x 4 mL).
7. Wash with brine (1 x 5 mL).
8. Dry organic layer with $CaCl_2$. Let stand for 5 minutes.

9. Filter or decant off the drying agent (the latter is much easier) into a tared, 50 mL Erlenmeyer flask.
10. Evaporate off the solvent with a gentle stream of air, using the now reduced hot plate temperature to aid in evaporation.
11. Recrystallize the resulting residue from water. Gently swirl flask, keeping the flask in contact with the plate, while allowing to dissolve.
12. Isolate product, and obtain an IR. Prep an NMR tube with d-chloroform as the solvent, label, and leave in beaker on common-use benchtop. These will be run for you. An IR and NMR of the starting acetaminophen will also be made available.
13. Obtain a melting point of phenacetin during limited-use lab hours.

**Clean-up**: Place all liquid waste in the liquid waste container. Turn off heater/stirrer before leaving.

Post-lab Questions:

1. In a Williamson-ether synthesis, why is the alkyl halide limited to methyl or primary?
2. What is something you would change if you were to perform this experiment again to increase your yield of product?
3. Draw the complete mechanism for the reaction performed in this experiment.
4. Working backwards, how would you synthesize the compound below using the Williamson-ether reaction?